Influence of exposure to climate-related hazards in the phenotypic expression of primary Sjögren's syndrome

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Abstract

Objective

To analyse how the key components at the time of diagnosis of the Sjögren's phenotype (epidemiological profile, sicca symptoms, and systemic disease) can be influenced by the potential exposure to climate-related natural hazards.

Methods

For the present study, the following variables were selected for harmonisation and refinement: age, sex, country, fulfilment of 2002/2016 criteria items, dry eyes, dry mouth, and overall ESSDAI score. Climate-related hazards per country were defined according to the OECD and included seven climate-related hazard types: extreme temperature, extreme precipitation, drought, wildfire, wind threats, river flooding, and coastal flooding. Climatic variables were defined as dichotomous variables according to whether each country is ranked among the ten countries with the most significant exposure.

Results

After applying data-cleaning techniques and excluding people from countries not included in the OECD climate rankings, the database study analysed 16,042 patients from 23 countries. The disease was diagnosed between 1 and 3 years earlier in people living in countries included among the top 10 worst exposed to extreme precipitation, wildfire, wind threats, river flooding, and coastal flooding. A lower frequency of dry eyes was observed in people living in countries exposed to wind threats, river flooding, and coastal flooding, with a level of statistical association being classified as strong ($p<0.0001$ for the three variables). The frequency of dry mouth was significantly lower in people living in countries exposed to river flooding ($p<0.0001$) and coastal flooding ($p<0.0001$). People living in countries included in the worse climate scenarios for extreme temperature ($p<0.0001$) and river flooding ($p<0.0001$) showed a higher mean ESSDAI score in comparison with people living in no-risk countries. In contrast, those living in countries exposed to worse climate scenarios for wind threats ($p<0.0001$) and coastal flooding ($p<0.0001$) showed a lower mean ESSDAI score in comparison with people living in no-risk countries.

Conclusion

Local exposure to extreme climate-related hazards plays a role in modulating the presentation of Sjögren across countries concerning the age at which the disease is diagnosed, the frequency of dryness, and the degree of systemic activity.

Key words

Sjögren's syndrome, dryness, systemic, ESSDAI, climate, epidemiology

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Introduction

Primary Sjögren's syndrome (SjS) is a systemic autoimmune disease that mainly affects middle-aged women and has a prevalence ranging between 0.01 and 0.72%. Aetiopathogenetically, SjS primarily targets the exocrine glands, which are infiltrated by lymphocytes (1). More than 95% of patients exhibit oral and ocular dryness but may also develop many extraglandular (systemic) involvement that may be the presenting manifestation.[2] The key immunological markers are anti-Ro antibodies (the most specific), cryoglobulins, and hypocomplementaemia (the core prognostic markers) (2).

The impact of climate change on human health is a pressing global issue with broad implications for future generations. Climate change poses a growing threat by influencing the intensity and, in some cases, the frequency of climate-related natural hazards (3). Extreme weather conditions induced by climate change have been associated with many diseases, such as heat-related illnesses, respiratory diseases, and mental health issues, contributing heavily to disrupting healthcare systems or facilitating food insecurity and malnutrition. While the impacts of climate change on health are undeniably threatening, they also provide an impetus to improve public health infrastructure and mitigate climate change by reducing greenhouse gas emissions.

Although the aetiopathogenesis of systemic autoimmune diseases remains complex, heterogeneous, and yet to be elucidated fully, some studies have started to evaluate the potential role of environmental factors. Unfortunately, the number of studies is limited, and most are focusing on the seasonal variations in disease incidence and how disease activity may be influenced by seasonally changing environmental factors (4-6). The studies focused on SjS are very few (7, 8). Understanding how environmental factors may influence the phenotype of SjS at diagnosis could support early identification of the disease and requires further investigations. In fact, wide individual variations in the phenotypic expression of systemic autoimmune diseases represent a relevant handicap in studies designed to identify homogeneous disease patterns that may aid early identification of disease (9). This is especially complicated in studies including few patients, as there is often a lack of significant between-group differences. However, this type of analysis is only possible when big data sources are used, including a sufficiently representative number of patients per country.

This study aimed to analyse how the key components of the disease phenotype at the time of diagnosis (epidemiological profile, sicca symptoms, and systemic disease) can be influenced by the potential exposure to climate-related natural hazards in the largest reported international, multi-ethnic cohort of patients with primary SjS.

Material and methods

Patients

The Big Data Sjögren Project Consortium is an international, multicentre registry created in 2014 to obtain a worldwide picture of the main features of primary SjS using a cooperative data-sharing cooperative merging of pre-existing clinical SjS databases from leading centers in clinical research in SjS from five continents (14). The centres share a harmonised data infrastructure and conduct cooperative online efforts to refine the data already collected in each centre. Databases from each centre are harmonised into a single database through the application of data-cleaning pre-processing techniques. The inclusion criteria met the 2002 and/or 2016 classification criteria for SjS (10). Exclusion criteria for considering SjS as a primary disease consisted of the presence of other systemic autoimmune diseases. The project was approved by the Ethics Committee of the Coordinating Centre (Hospital Clinic, Barcelona, Spain, registry HCB/2015/0869).

Definition of variables

By January 2023, the participant centres had included 16,679 patients from 27 countries. The main disease features at diagnosis were collected and analysed retrospectively. For the present study, the following clinical variables were selected for harmonisation and refinement: age, sex, country, fulfilment of items from the 2002/2016 criteria, presence of dry eyes, dry mouth, and overall ESSDAI score. Age at diagnosis was defined based on the moment the attending physician confirmed compliance with the 2002 or 2016 criteria. Systemic involvement at diagnosis was classified and scored using the ESSDAI classification (11).

Climate-related hazards per country were defined in accordance with OECD Environment Working Paper No. 201, "Monitoring exposure to climate-related hazards: indicator Methodology and key results" (12). The OECD defined seven climate-related hazard types: extreme temperature, extreme precipitation, drought, wildfire, wind threats, river flooding, and coastal flooding. The results were presented for 52 IPAC countries classified for each climate-related hazard according to the following definitions (Supplementary Table S1). Exposure to extreme temperature ranking is based on the (1) average annual share of population exposure to hot days (Tmax >35°C), (2) average annual share of population exposure to tropical nights (Tmin >20°C), and (3) average annual number of days with heavy heat stress (UTCI >32°C). Extreme precipitation ranking is based on the average annual share of cropland exposed to more than seven days with extreme precipitation events (total precipitation >99th percentile of the reference period). Drought ranking is based on the average cropland soil moisture anomaly. Wildfire ranking is based on the average annual population percentage and forests in wildfire-prone areas. Wind threat ranking is based on population and built-up exposure to a violent storm or worse (wind gusts >28.6 m/s). The classification of river and coastal flooding ranking is based on the percentage of built-up area exposed to river or coastal flooding over 100-year.

Statistical analysis

The key determinants that defined the disease phenotype at diagnosis (age, female-to-male ratio, dry eyes, dry mouth, and systemic disease) were classified as dependent variables. The OECD climate-related hazard types (extreme temperature, extreme precipitation, drought, wildfire, wind threats, river flooding, and coastal flooding) were classified as independent variables. Climatic OECD variables were defined as dichotomous variables according to whether each country is ranked (yes or not) among the ten countries with the most significant exposure. Data cleaning was performed to ensure the accuracy and integrity of the dataset. The frequency of observations in each non-numeric category was analysed, and the characteristics of numeric variables were reviewed. This process helped identify and correct inconsistencies and miscoded values. The chi-square test of independence was used to analyse the association between categorical variables. The results were presented in tables with frequencies provided as the number of observations and the percentage of the total for each category. Independent two-sample t-tests were applied to compare categorical and continuous variables. The Point-Biserial correlation coefficient was calculated to measure the relationship between the male-to-female ratio and continuous variables. Considering the large sample size in the study, we used a significance level of 0.0001 for these tests to assess a strong statistical association. A p-value between 0.0001 and 0.05 was considered a weak statistical association. All analyses were conducted by MRC using ChatGPT 4.0 Code Interpreter as copilot, which used Python and the libraries *Pandas, Numpy, Scipy, Matplotlib, Seaborn,* and *Sklearn*. The code was written and executed in an environment with internet access turned off to ensure privacy and data security using a Jupyter notebook, an open-source web application.

Results

After applying data-cleaning techniques and excluding patients from countries not included in the OECD climate rankings, the database study comprised 16,042 cases from 23 countries. The baseline characteristics of the cohort are summarised in Table I and included 14,987 (93.4%) women with a mean age at diagnosis of primary SjS of 51.74 (SD 14.47) years. The frequencies of sicca symptoms were 90.9% for dry eye and 92.1% for dry mouth. The mean ESSDAI score at diagnosis for the entire cohort was 6.92 (SD 7.49).

Table I. Baseline characteristics of the cohort.

Variable	Overall (n=16042)
Gender	
Women	14987 (93.4%)
Men	1055 (6.6%)
Age	
Mean (SD)	51.740 (14.466)
Range	5.000 - 97.000
Dry eyes	
No	1454 (9.1%)
Yes	14588 (90.9%)
Dry mouth	
No	1268 (7.9%)
Yes	14774 (92.1%)
ESSDAI score	
N-Miss	582
Mean (SD)	6.918 (7.494)
Range	0.000 - 87.000
Extreme temperature exposition	
No	8868 (55.3%)
Yes	7174 (44.7%)
Extreme precipitation	
No	13591 (84.7%)
Yes	2451 (15.3%)
Drought	
No	12844 (80.1%)
Yes	3198 (19.9%)
Wildfire	
No	9512 (59.3%)
Yes	6530 (40.7%)
Wind threat	
No	13133 (81.9%)
Yes	2909 (18.1%)
River flooding	
No	12681 (79.0%)
Yes	3361 (21.0%)
Coastal flooding	
No	12061 (75.2%)
Yes	3981 (24.8%)

Influence of extreme climate on demographic profile

The correlation results for the relationship between the male-to-female ratio and each climate variable showed that all p-values are above 0.05, indicating that none of the correlations were statistically significant at the 5% level (Suppl. Table S2).

Table II shows the mean age at diagnosis and the standard deviation of the age according to the country-ranked exposure to extreme climate. The mean age at diagnosis was significantly low-

Table II. Mean age at diagnosis and the standard deviation of the age according to the country-ranked exposure to extreme climate.

Climate variable	Ranking of 10 countries worse exposed	Mean age (years)	Difference (years)	Standard deviation (years)	Number of observations	T statistic	*p*-value
Extreme temperature	Yes	51.89	0.18	14.53	7174		
	No	51.61		14.42	8868	-1.22	0.2235
Extreme precipitation	Yes	50.2	-1.41	13.53	2451		
	No	52.02		14.61	13591	5.72	<0.0001
Drought	Yes	51.25	-0.77	14.72	3198		
	No	51.86		14.4	12844	2.15	0.0318
Wildfire	Yes	50.66	-1.2	14.56	6530		
	No	52.48		14.35	9512	7.83	<0.0001
Wind threat	Yes	50.75	-1.73	14.86	2909		
	No	51.96		14.37	13133	4.09	<0.0001
River flooding	Yes	49.54	-2.42	14.37	3361		
	No	52.32		14.44	12681	9.97	<0.0001
Coastal flooding	Yes	49.77	-2.55	14.64	3981		
	No	52.39		14.35	12061	9.92	<0.0001

er in those countries with the worst climate exposure (among the top 10 OECD ranking) to extreme precipitation, drought, wildfire, wind threats, river flooding, and coastal flooding (Fig. 1). The disease was diagnosed between 1 and 3 years earlier in people living in countries included among the top 10 worst exposed to extreme precipitation, wildfire, wind threats, river flooding, and coastal flooding (Fig. 2).

Influence of extreme climate on dryness

Table III presents the results of the chi-square tests of independence for each climate-related variable with the frequency of dry eyes at diagnosis. All variables except WF showed *p*-values <0.05. A higher frequency of dry eyes was observed in people living in countries exposed to extreme temperatures (*p*-value=0.0003), extreme precipitations (*p*-value=0.02), and extreme drought (*p*-value=0.03). However, the level of statistical association was classified as weak (*p*-value between 0.0001 and 0.05). In contrast, the frequency of dry eyes was significantly lower in people living in countries exposed to wind threats, river flooding, and coastal flooding, with a level of statistical association being classified as strong (*p*-value <0.0001 for the three variables) (Fig. 3).

Table IV presents the results of the chi-square tests of independence for each climate-related variable with the

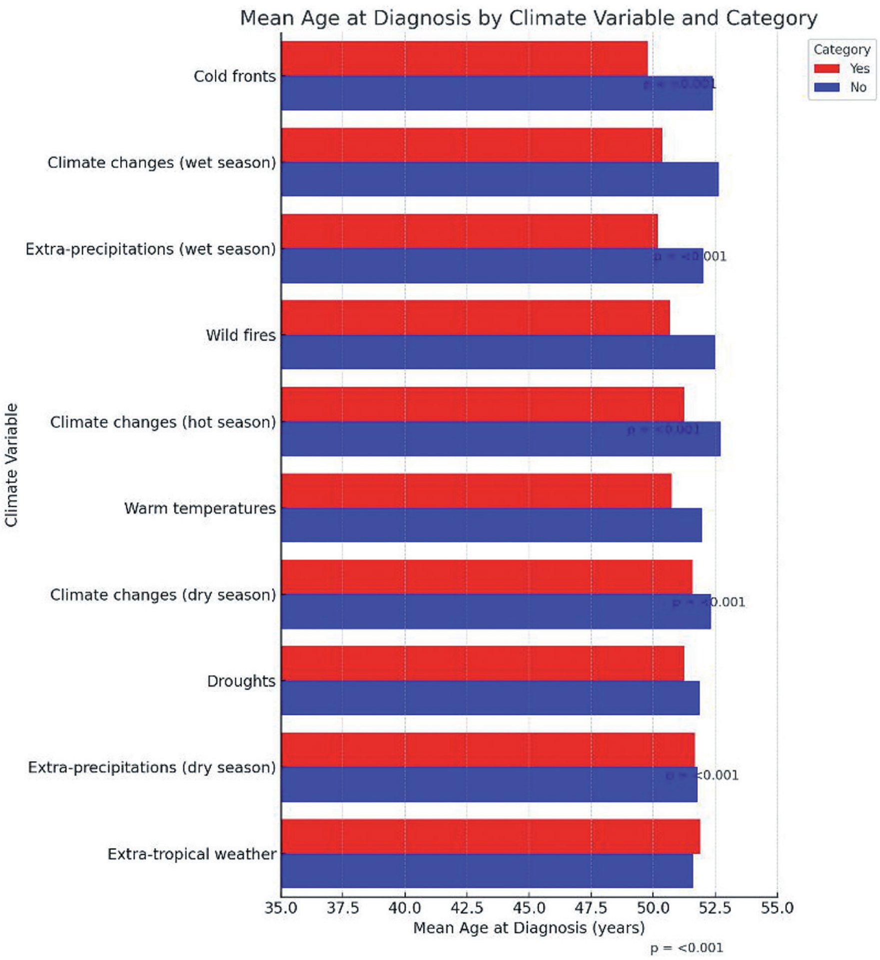

Fig. 1. Mean age at diagnosis according to the country-ranked exposure to extreme climate (red bar, mean age from people living in countries included among the top 10 worst exposed to climate-related hazard; blue bar, people living in other Countries).

frequency of dry mouth at diagnosis. A higher frequency of dry mouth was observed in people living in countries exposed to extreme temperatures (*p*-value <0.0001) and extreme drought (*p*-value = 0.0002), In contrast, the frequency of

Table III. Results of the chi-square tests of independence for each climate-related variable with the frequency of dry eyes at diagnosis.

Climate Variable	Ranking of 10 countries worse exposed	Dry eyes	Lack of dry eyes	Chi-square	*p*-value
Extreme temperature	Yes	6590 (91.86%)	584 (8.14%)		
	No	7998 (90.19%)	870 (9.81%)	1,321,785	0.00028
Extreme precipitation	Yes	2259 (92.17%)	192 (7.83%)		
	No	12329 (90.71%)	1262 (9.29%)	5,137,044	0.02342
Drought	Yes	2940 (91.93%)	258 (8.07%)		
	No	11648 (90.69%)	1196 (9.31%)	465,925	0.03089
Wildfire	Yes	5914 90.57%)	616 (9.43%)		
	No	8674 (91.19%)	838 (8.81%)	175,114	0.18573
Wind threat	Yes	2549 (87.62%)	360 (12.38%)		
	No	12039 (91.67%)	1094 (8.33%)	4,679,202	*p*<0.00001
River flooding	Yes	2927 (87.09%)	434 (12.91%)		
	No	11661 (91.96%)	1020 (8.04%)	7,583,834	*p*<0.00001
Coastal flooding	Yes	3349 (84.12%)	632 (15.88%)		
	No	11239 (93.18%)	822 (6.82%)	29,698,349	*p*<0.00001

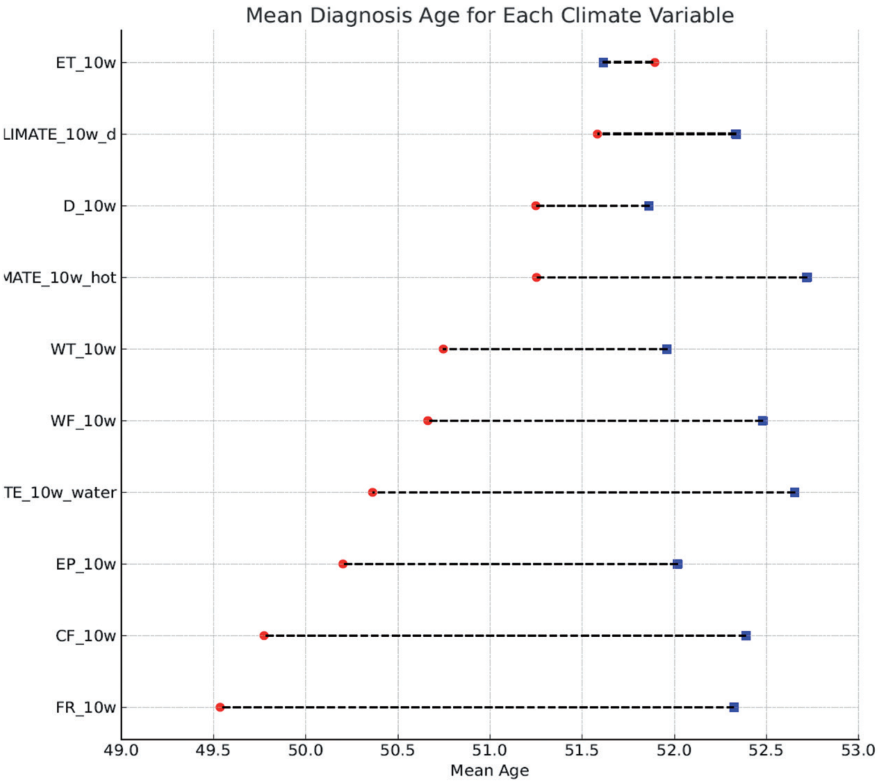

Fig. 2. Mean age at diagnosis in people living in countries included among the top 10 worst exposed to climate-related hazards (red dot) in comparison with people living in other countries (blue dot).

dry mouth was significantly lower in people living in countries exposed to river flooding (*p*-value <0.0001) and coastal flooding (*p*-value <0.0001), with a level of statistical association being classified as strong (Fig. 4).

Influence of extreme climate on systemic disease

Table V presents the results of the t-tests comparing the mean ESSDAI scores measured at the time of diagnosis according to the country-ranked exposure to each extreme climate-related hazard. For some variables (extreme precipitation and drought), the differences are not statistically significant (*p*-value >0.05). People living in countries included in the worse climate scenarios for extreme temperature (*p*-value <0.0001) and river flooding (*p*-value <0.0001) showed a higher mean ESSDAI score in comparison with people living in no-risk countries (Fig. 5). In contrast, those living in countries exposed to worse climate scenarios for extreme precipitation (*p*-value=0.048), wildfire (*p*-value=0.001), and, especially, wind threats (*p*-value <0.0001) and coastal flooding (*p*-value <0.0001), showed a lower mean ESSDAI score in comparison with people living in no-risk countries (Fig. 6).

Discussion

Exposure to extreme climate is considered a global health risk factor (13). The effects of exposure to extreme climate change impact people's health through direct effects (causing diseases and worsening pre-existing conditions) and indirect effects that negative interfere with people's daily activities. Extreme heat and cold are critical climate-related hazards for many human activities, including human health, agriculture, transport, and energy. Droughts can result in severe impacts on agriculture, energy, and water management sectors and society as a whole; annual and seasonal precipitation patterns influence a wide range of human, social, and economic activities; flooding can cause financial losses through its impacts on energy and transport infrastructures, human settlements and agricultural land, wind threats have direct implications for humans, ecosystems and economic infrastructures, and wildfires impacts on forestry, agriculture, tourism, transport, infrastructure, water

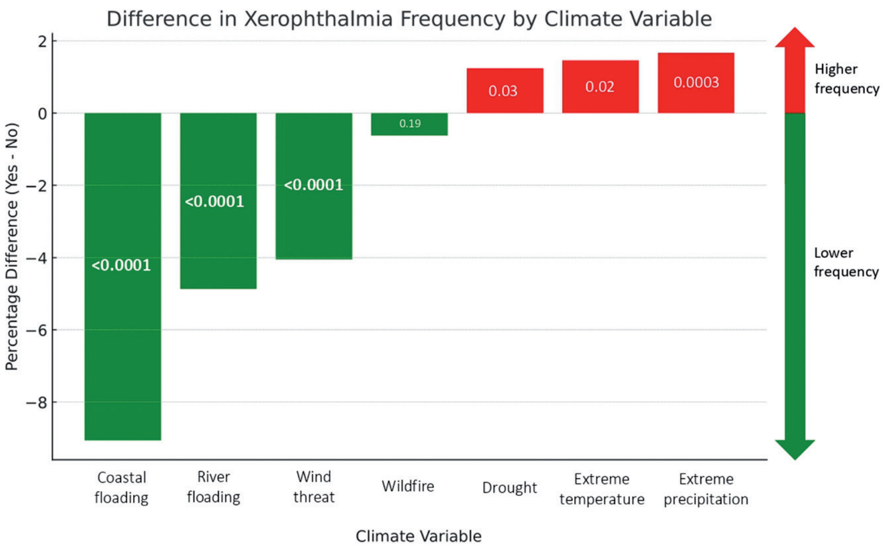

Fig. 3. Percentage difference in the frequency of xerophthalmia in people living in countries included among the top 10 worst exposed to climate-related hazards in comparison with people living in other countries.

supply, biodiversity, wildlife and human health (3, 12).

Existing research highlights the multifactorial interplay between genetic and environmental factors as key aetiopathogenetic factors favouring the development of autoimmune diseases, including determinants closely linked to the local or personal environment (14). Among them, climate and seasonal changes have been increasingly associated with the onset and severity of various autoimmune diseases. On the one hand, some studies have shown correlations between climatic factors and the beginning of autoimmune conditions. Seasonal weather influences the incidence rate of sarcoidosis in specific geographical areas, with the peak of the diagnosed cases varying widely month-by-month (15, 16). Other studies have suggested that vitiligo diagnoses are more prevalent during the summer months, while type 1 diabetes has a higher incidence during winter (17). On the other hand, a growing body of evidence suggests that disease activity may be influenced by seasonally changing environmental factors. Multiple sclerosis relapses tend to increase during spring and summer (18), and cyclic seasonal variations have been linked to activity and symptom exacerbation in systemic lupus erythematosus, vasculitis, and inflammatory myopathies (19-21).

Personal determinants, closely connected to the local environment, are also involved in the pathogenesis of primary SjS (22). Evidence for the critical role of lifestyle and environmental factors is increasing, including a potential influence of diet (23, 24), soil metals (25), seasonality (7), and air pollution (26). We recently reported that the significant variability in the presentation of systemic SjS is strongly linked with geoepidemiological personal determinants such as age, gender, ethnicity, and place of residence (27).

For the first time, the study we present reports the significant influence of extreme climatic conditions on the phenotypic expression of SjS at an international scale. Regarding demographic profile, we find no statistically significant correlation between the male-to-female ratio and the climatic variables. Nevertheless, a significant correlation was observed between the age at SjS diagnosis and climatic exposure. Specifically, people from countries facing high vulnerability to extreme climatic events are diagnosed 1 to 3 years earlier than in other countries. This suggests that these environmental factors might hasten the onset of disease detection in such regions. Age at diagnosis is one of the strongest determinants influencing how SjS is expressed at diagnosis. Age at diagnosis is also a key determinant of the expression of systemic disease in

Table IV. Results of the chi-square tests of independence for each climate-related variable with the frequency of dry mouth at diagnosis.

Climate Variable	Ranking of 10 countries worse exposed	Dry mouth	Lack of dry mouth	Chi-square	*p*-value
Extreme temperature	Yes	6625 (92.35%)	549 (7.65%)		
	No	8149 (91.89%)	719 (8.11%)	1,067,025	0.30162
Extreme precipitation	Yes	2259 (94.74%)	129 (5.26%)		
	No	12452 (91.62%)	1139 (8.38%)	27,294,968	p<0.00001
Drought	Yes	2940 (93.71%)	201 (6.29%)		
	No	11777 (91.69%)	1067 (8.31%)	14,107,202	0.00017
Wildfire	Yes	6031 (92.36%)	499 (7.64%)		
	No	8743 (91.92%)	769 (8.08%)	0.98328	0.32139
Wind threat	Yes	2549 (91.92%)	235 (8.08%)		
	No	12100 (92.13%)	1033 (7.87%)	0.120225	0.72879
River flooding	Yes	2927 (87.21%)	430 (12.79%)		
	No	11843 (93.39%)	838 (6.61%)	138,792,515	p<0.00001
Coastal flooding	Yes	3563 (89.50%)	418 (10.50%)		
	No	11211 (92.95%)	850 (7.05%)	48,533,005	p<0.00001

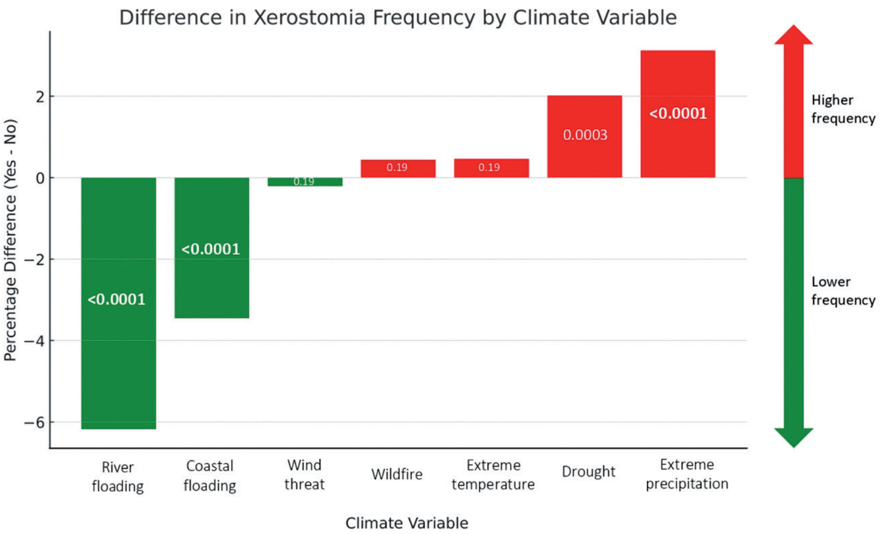

Fig. 4. Percentage difference in the frequency of xerostomia in people living in countries included among the top 10 worst exposed to climate-related hazards in comparison with people living in other countries.

Table V. Results of the t-tests comparing the mean ESSDAI scores measured at the time of diagnosis according to the country-ranked exposure to each extreme climate-related hazard.

Climate variable	Ranking of 10 countries worse exposed	Mean ESSDAI score	t-statistic	*p*-value
Extreme temperature	Yes	7.53	10.28	<0.00001
	No	6.3		
Extreme precipitation	Yes	6.64	-1.73	0.08387
	No	6.89		
Drought	Yes	6.89	-1.34	0.17914
	No	7.07		
Wildfire	Yes	6.77	-3.22	0.00128
	No	7.15		
Wind threat	Yes	5.68	-11.23	<0.00001
	No	7.11		
River flooding	Yes	8.27	9.77	<0.00001
	No	6.56		
Coastal flooding	Yes	5.96	-9.87	<0.00001
	No	7.14		

primary SjS, and we have recently reported that the highest systemic scores were reported for patients diagnosed before age 35, and that age also modulated the increase in activity in each organ (9).

The frequency of dryness symptoms displayed significant variations based on climatic exposures. Individuals diagnosed in countries with pronounced extreme temperatures and drought had a higher prevalence of dryness at diagnosis, though these associations were weak. Conversely, people from countries facing significant river and coastal flooding registered significantly lower frequencies. No previous studies focused on the influence of exposure to extreme climate on the frequency of reported dryness at the time of diagnosis of SjS. However, some previous studies have investigated the potential impact of seasonality on dry mouth and dry eyes. One study did not reveal any seasonal influence on the primary symptoms of SjS (pain, fatigue, and dryness) (7). In contrast, a case-control study including 27 patients with subjective symptoms of dry mouth (15 had SjS) suggested that specific dry mouth symptoms are exacerbated following seasonal patterns (need to drink during the daytime higher in winter and swallowing, talking difficulties, and oral pain in summer) (8). A study involving dry eye disease patients, including those with SjS, found that 47% of patients reported a high seasonal-related impact on their eye symptoms, with more prominent effects during winter and summer and milder effects in autumn and spring (28). Key weather factors such as sunshine, heat, cold, and seasonal combinations affect the perception of dry eye symptoms, showing a relationship between longer sunshine duration/lower humidity and the prevalence of dry eye disease. These studies underscored psychrometry principles' significance in understanding the water vapor and air mixture's impact on thermal comfort in heating, ventilating, air conditioning, and meteorology (28). Our results are in line with previous findings as we find that people living in countries exposed to flooding have lower frequencies of dryness at diagnosis, following the hypothesis that high humidity environment may contribute to some patients not reporting the sensation of dryness to a sufficient degree to refer it a health problem.

Rain and fog have been reported as aggravating factors, and increased relative humidity in high-humidity areas could influence the sensation caused by dry eye due to thermal comfort. This can be explained by considering that while excess moisture, as in fog, might aggravate symptoms, decreased environmental humidity could trigger subjective complaints. Humidity varies with the seasons, and relative humidity, which represents the ratio of the actual amount of water vapor present to the total capacity of air to contain water vapor at a particular moment and temperature, plays a crucial role. Relative humidity increases with lower temperatures and decreases with higher temperatures. The lack of aggravating effects of rain and fog on dry eye symptoms may be related to the dew point, which could even alleviate the symptoms (28). Hence, the geographical variation of dew point emerges as a significant consideration for patients prone to present with dry eye symptoms. Although some studies have reported a positive

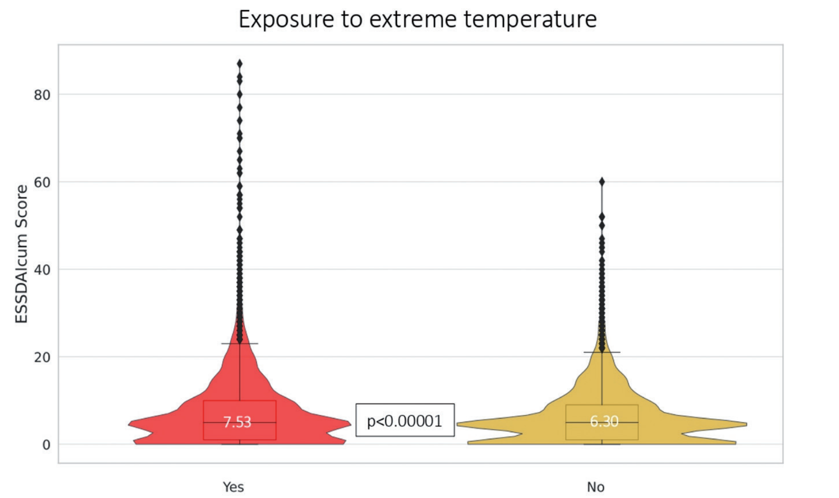

Fig. 5a. Mean ESSDAI score at diagnosis in people living in countries included in the worse climate scenarios for extreme temperature (red) in comparison with people living in no-risk countries (green).

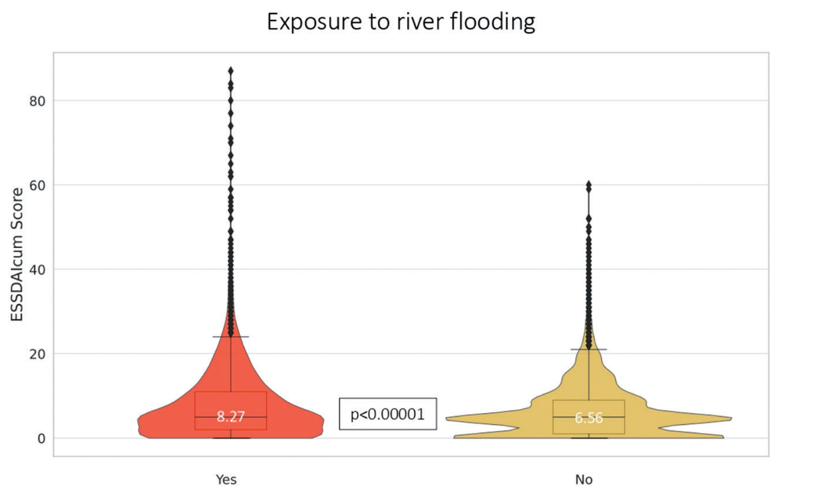

Fig. 5b. Mean ESSDAI score at diagnosis in people living in countries included in the worse climate scenarios for exposure to river flooding (red) in comparison with people living in no-risk countries (green).

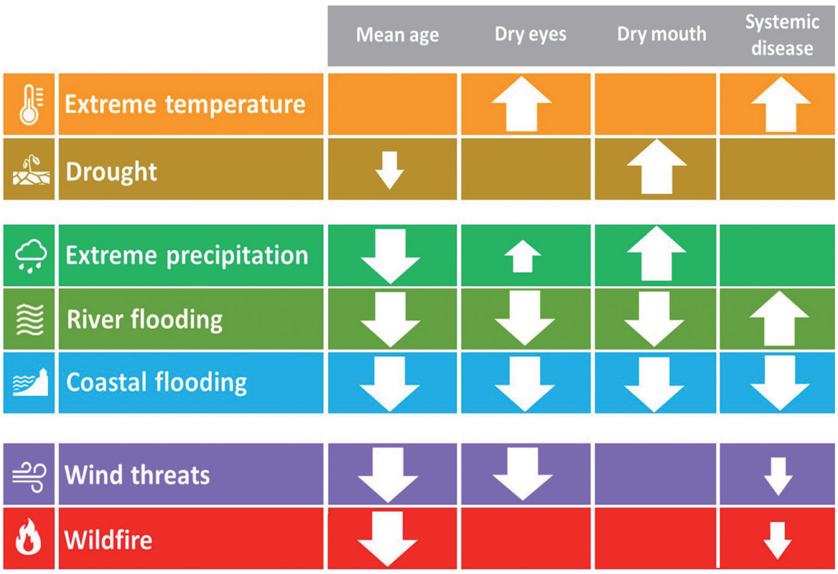

Fig. 7. Visual abstract summarising the statistically significant associations between the key features defining SjS at diagnosis and the exposure to climate-related hazards.

correlation between windy weather and eye dryness (29), our results did not show a strong correlation. Although windy conditions have not been definitively identified as a risk factor for dry eye sensation, the theoretical basis for this association is straightforward: dry eye conditions often exhibit increased evaporation rates (30).

The systemic manifestation of the disease, represented by the ESSDAI score at diagnosis, revealed distinct correlations based on climatic exposures. People from countries affected by extreme temperatures and river flooding presented with a higher mean ESSDAI score, indicating more severe systemic manifestations. On the other hand, regions more exposed to threats from wildfires, wind threats, extreme precipitation, and coastal flooding had individuals with a lower mean ESSDAI score. Only a previous study investigated the potential role of personal determinants in how systemic disease is expressed at the time of SjS diagnosis. We reported that the systemic phenotype of primary SjS is strongly influenced by personal determinants such as age, gender, ethnicity, and place of residence, which are key geoepidemiological players in driving the expression of systemic disease at diagnosis, with systemic activity measured by the ESSDAI, clinical ESSDAI (clinESSDAI) and disease activity states was higher in patients from southern countries ($p<0.001$) (27).

Despite being conducted in the largest international cohort of patients with SjS published so far, this is an exploratory study whose results must be interpreted considering the limitations inherent in the methodological approach. Concerning climatic variables, significant gaps exist in the international exchange of observations on hydro-meteorological events, particularly in Least Developed Countries and Small Island Developing States, and because the data are based on national averages, it hides more severe local impacts of climate-related hazards (3, 12). In addition, the data does not provide temporal information on the onset of symptoms, so we cannot determine whether the climate conditions preceded the onset of the disease.

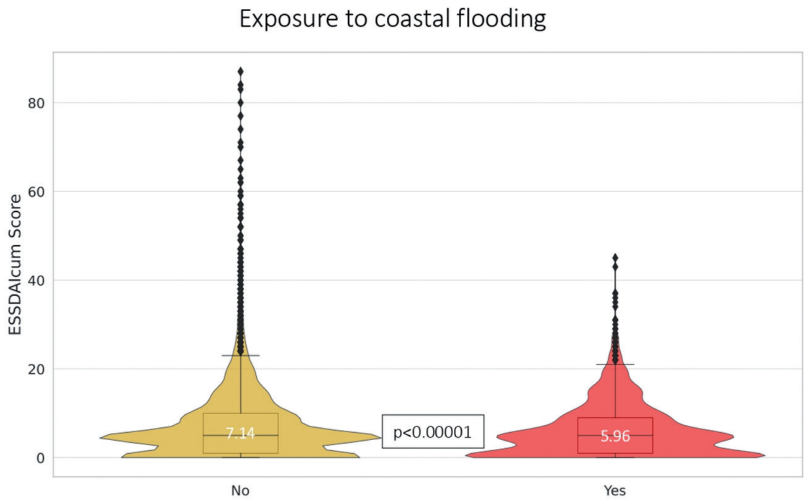

Fig. 6a. Mean ESSDAI score at diagnosis in people living in countries included in the worse climate scenarios for exposure to coastal flooding (red) in comparison with people living in no-risk countries (green).

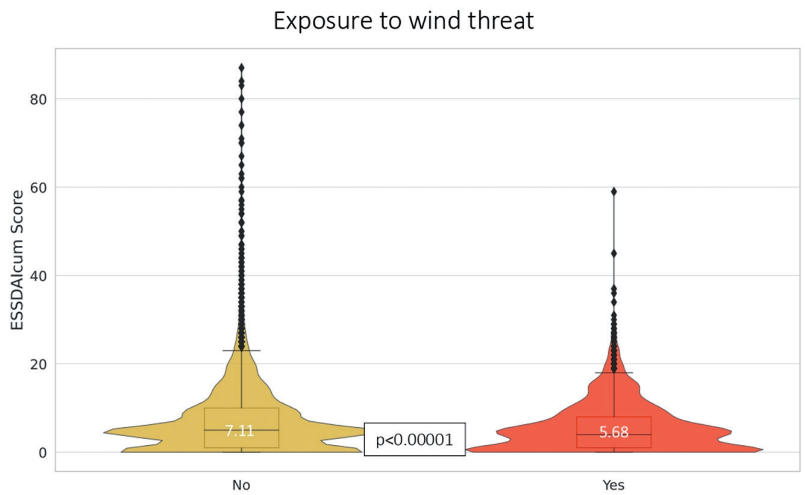

Fig. 6b. Mean ESSDAI score at diagnosis in people living in countries included in the worse climate scenarios for exposure to wind threats (red) in comparison with people living in no-risk countries (green).

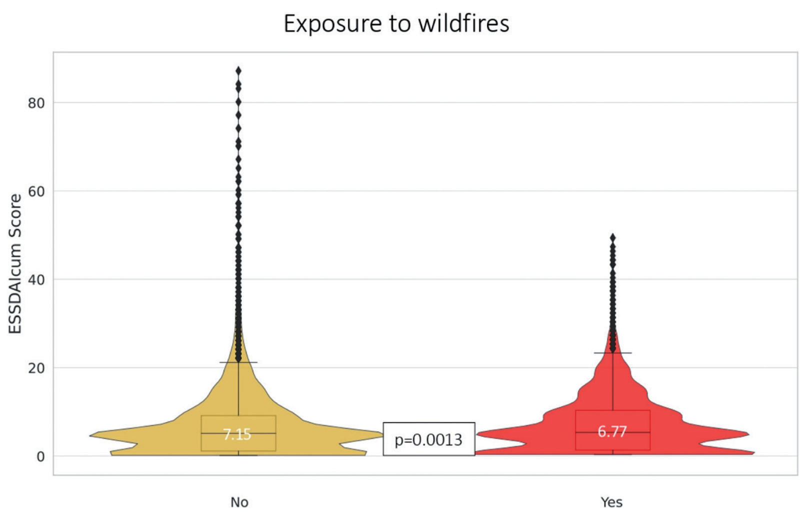

Fig. 6c. Mean ESSDAI score at diagnosis in people living in countries included in the worse climate scenarios exposure to wildfires (red) in comparison with people living in no-risk countries (green).

In addition to the influence of personal determinants as covariates, while raw proportions are used, they do not account for potential confounding factors as many other factors may influence dependent variables. That correlation does not imply causation, and the results should be interpreted cautiously. Finally, and as in any exploratory observational study, it is essential to distinguish between association and causality when interpreting the results and remember that these results indicate associations, not causations. It is necessary to conduct more detailed studies, with a more focused geographical detail, and use longitudinal data, to further confirm these associations and their possible implications. A multivariate analysis could be performed for a more comprehensive understanding of the relationship between climate conditions and xerophthalmia.

In conclusion, we reported a significant influence of climatic conditions on the phenotypic expression of SjS at diagnosis (Fig. 7). Local exposure to extreme climate-related hazards plays a role in modulating the presentation of primary SjS across countries concerning the age at which the disease is diagnosed, the frequency of dryness, and the degree of systemic activity. This knowledge can provide valuable insights for clinical strategies in regions with pronounced climatic exposures, potentially aiding in earlier detection and intervention.

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